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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,281	12/21/2001	John Wyrick	10050560-1	4057

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/032,281	WYRICK ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,15-17,87,88 and 90-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,15-17,87,88 and 90-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 28, 2006 has been entered.

Claim Rejections - 35 USC § 112

2. Claims 1-6, 8, 15-17, 87, 88 and 90-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The new limitation of "labeling a second portion of the mixture produced in b) with a second fluorescent label to produce a control sample" in claim 1 is apparently new matter. Applicant's response pointed to two places for support. A careful review by the examiner of the cited pages of the specification failed to identify any support for the new limitation.

In particular, the first cited place, figure 1, shows no support for controls whatsoever. The second citation, to page 16, lines 5-20, clearly discusses the use of controls, as reproduced below.

> The methods of the present invention can further comprise comparing the results to a control (control sample). For example, in one embodiment, the methods of the present invention can be carried out using a control protein which is not a DNA binding protein. In one embodiment, immunoprecipitation is performed using an antibody against an HA or MYC epitope tag. The results of immunoprecipitating the protein of interest containing the tag, and the protein of interest without the tag are compared. The untagged protein should not be immunoprecipitated, and thus, serves as a negative control. Using the methods of the present invention also provides for the ability to compare the sample with the control sample simultaneously. Generally, a test sample if hybridized to an array and compared to a control sample which has been hybridized to a different array and a ratios is calculated to determine binding results. Using the methods described herein, two samples (*e.g.*, a test sample and a control sample) can be hybridized to the same array which allows for elimination of noise due to the use of two arrays (*e.g.*, an array for the test sample and another array for the control sample). The difference between arrays due to manufacturing artifacts is a major source of noise, which can be eliminated using the methods described herein.

The problem is that the cited section never discusses labeling the mixture produced in step b). All controls are not created equal and discussion of one control, even a generic control, does not provide descriptive support for all possible controls. The test in description is possession, not enablement. In the current case, the disclosed control at page 16 is either using a protein which is not a DNA binding protein or against tagged and untagged protein. There is no discussion of any "second portion" at all in the

specification. A word search (using an OCRed text) of the specification failed to find any support for the use of such a second portion as a control in the entire specification. If there is actual specific support for this concept, Applicant is requested to specifically identify it in the specification.

Claim Interpretation

3. Several of the terms in the claims lack specific definitions in the specification and are broadly interpreted. The term "intergenic" is interpreted as any region in the genome which is "between two genes" where a gene is an open reading frame. The term "microarray" is simply any substrate with which a nucleic acid can be hybridized and can include a southern blot.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-6, 8, 15-17, 87, 88 and 90-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orlando et al (Methods (1997) 11:205-214) in view of Schena (Tibtech (1998) 16:301-306).

Orlando teaches a method of claims 1, 10, 11 and 71 for identifying a region of a genome of a cell to which a protein of interest binds (see abstract) comprising the steps of:

a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see figure 1 and page 205-206, subheading "1. In vivo Formaldehyde fixation of cells"),

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see figure 1 and page 206, subheading "2. Chromatin solubilization by sonication"),

c) removing a DNA fragment to which the protein of interest is bound from a first portion the mixture produced in b) (see figure 1 and page 209, subheading "5. Immunoprecipitation of crosslinked chromatin", where the first portion is that immunoprecipitated with the anti-Pc antiboides (see figure 6, for example)),

d) separating the DNA fragment identified in c) from the protein of interest (see figure 1 and page 210, subheading "6. Reversal of cross-links and DNA purification"),

e) labeling the DNA fragment of d) with a first label (see figure 1 and page 210-211, subheading "9. Southern analysis and mapping of binding sites in DNA", where the separated DNA is labeled with ^{32}P-dCTP),

f) labeling a second portion of the mixture produced in b) with a label to produce a control sample (see figure 6 and page 210-211, subheading "9. Southern analysis and mapping of binding sites in DNA, where the fragmented DNA was immunoprecipitated without antibodies to serve as a control (see page 213, column 1)).

g) combining the DNA fragment of e) and the control sample of f) with a Southern blot (which is a crude form of microarray as discussed previously)(see figure 6 and page 213, column 1) which comprising more than one sequence complementary to more than one intergenic regions of genomic DNA of the cell under conditions in which hybridization between the DNA fragments and a sequence complementary to an intergenic region of the genomic DNA occurs (see figure 1 and subheading "9. southern analysis and mapping of binding sites in DNA" where the figures 6 and 7 demonstrate that multiple sequences of multiple intergenic regions are on the blot as shown by the presence of probes such as probe 2206 which is between the ultrabithorax and abdominal-A genes),

h) comparing results obtained from said first label to results obtained from said control sample to identify the sequences of g) to which the DNA fragment hybridizes, whereby the region identified in h) is the region of the genome in the cell to which the protein of interest binds (see figures 6 and 7 and page 213, column 1, especially where Orlando expressly compares the label to the control, stating"

> One problem in such a quantification is to determine the level at which hybridization rises above background and is specific to the immunoprecipitation. For regions where the enrichment is large (for example in Polycomb immunoprecipitations), this background becomes negligible; however, the signal-to-background ratio may become significant in cases where a particular sequence is only weakly enriched during the immunoprecipitation. For example, if genomic DNA is hybridized for long periods to the genomic walk, a uniform hybridization of all bands may be seen. A number of solutions to this problem can be suggested. First, if sequences are known that do not interact with the protein of interest, then the amount of hybridization to these sequences can set the background level. Alternatively the signals generated from hybridizing DNA from control immunoprecipitations (labeled to the same specific activity) can be quantified and subtracted from the values of the actual immunoprecipitation.

This statement expressly teaches comparing the label of the control immunoprecipitation to the label of the test sample in order to identify which signals are meaningful.

With regard to claims 1, Orlando teaches hybridization to a southern blot, which is a type of microarray as discussed above (see figure 6).

With regard to claims 2, Orlando teaches the use of Drosophila melanogaster cells which are eukaryotic (see page 205, column 1).

With regard to claims 3, Orlando teaches the use of DNA binding transcription factors (see page 213, column 2).

With regard to claims 4, Orlando teaches crosslinking with formaldehyde (see page 205-206, subheading "1. In vivo Formaldehyde fixation of cells").

With regard to claims 5, Orlando teaches the use of antibodies to bind the protein of interest (see page 209, subheading "5. Immunoprecipitation of crosslinked chromatin").

With regard to claims 6, 90 and 91, Orlando teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see page 210-211, subheading "8. Amplification of immunoprecipitated DNA by linker modified DNA PCR").

With regard to claims 8, Orlando teaches the use of a control (see figure 7, figure legend "The white bars indicate the fragments containing repetitive elements (M-repeats) that hybridized also with the control fraction").

With regard to claims 17, Orlando teaches shearing the DNA to make fragments (see page 206, subheading "2. Chromatin solubilization by sonication").

With regard to claims 87, Orlando teaches identifying a DNA binding site of the protein where the protein is a transcription factor (see figure 1, page 211, column 2 and figures 6 and 7).

Orlando does not teach the use of two colors of fluorescent labels to compare the control and test samples in the place of the radioactive samples and Orlando does not teach a traditional "microarray", teaching only the use of Southern blots.

Schena teaches the use of two colors of fluorescent labels to multiplex samples on microarrys (see page 301 to page 302).

With regard to claims 15 and 16, Schena expressly teaches fluorescent labeling, showing a Cy5 fluorescently labeled microarray in figure 3.

Schena teaches the use of microarrays to analyze genomic information (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent labels of Schena for the radioactive labels of Orlando since Schena expressly indicates that fluorescent labeling is advantageous since "Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)." This same logic would apply to the method of Orlando, since while Orlando does perform the hybridization to the same support, the hybridization does not occur at the same time under precisely the same reaction conditions, and an ordinary practitioner would recognize, from the motivation of Schena, that the use of two fluorescent labels would permit multiplexing the analysis under precisely the same conditiosn, eliminating many of the complicating factors in the analysis. Further, an ordinary practitioner would have been motivated to perform the substitution of the microarrays of Schena for the Southern blot of Orlando since Schena expressly notes "Although reminiscent of filter based assays, chip assays are a fundamental departure from techniques that employ porous membranes. Chips allow true parallelism,

miniaturization, multiplexing and automation, and these key features provide a set of performance specifications that cannot be achieved with the earlier technologies (see page 301, column 2)." Schena is expressly teaching that chip assays are superior to the prior art filter based assays such as Southern blots of Orlando. Schena provides significant additional motivation to use microarrays in the place of such filter based assays noting,

> "Microarray assays allow massive parallel data acquisition and analysis. Parallelism greatly increases the speed of experimental progress and allows meaningful comparisons to be made between the genes or gene products represented in the microarray. Microarray assays may eventually allow the analysis of the entire human genome in a single reaction, and recent gene-expression experiments in yeast represent an important step towards this goal. Miniaturization of conventional assays is a general trend in biomedical research. Microscale assays reduce reagent consumption, minimize reaction volumes, increase the sample concentration and accelerate the reaction kinetics. Chip-based assays allow sensitive and rapid data detection with either confocal scanners or cameras equipped with charged-coupled devices. Although current microarray assays focus on nucleic acid hybridization, future studies will undoubtedly involve the parallel analysis of proteins, lipids, carbohydrates and small molecules. Multiplexing, the process by which multiple samples are analysed in a single assay, is another enabling feature of the microarray approach. Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)."

An ordinary practitioner, motivated by Orlando to analyze genomic nucleic acids in order to identify regions of protein binding, would have been motivated by Schena to substitute the use of a microarray for the southern blot since Schena teaches that

microarrays are faster, provide more meaningful comparisons, reduce reagent consumption and accelerate reaction kinetics, as well as increasing accuracy as discussed by Schena above.

Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Orlando the entire genome, as required by claims 88 and 92, in order to analyze the location of transcription factors on the entire genome simultaneously. This is particularly obvious in light of Schena, who teaches analysis of genomic samples.

7. Claims 1-6, 8, 15-17, 87, 88 and 90-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercola (U.S. Patent 6,410,233) in view of Hacia et al (Nucleic Acids Research (1998) 26(16):3865-3866) and further in view of in view of Schena (Tibtech (1998) 16:301-306).

Mercola teaches a method of claims 1 for identifying a region of a genome of a cell to which a protein of interest binds (see abstract) comprising the steps of:

a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see figure 1),

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see figure 1),

c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b) (see figure 1),

d) separating the DNA fragment identified in c) from the protein of interest (see figure 1),

e) labeling the DNA fragment of d) (see figure 1 and column 17, lines 55-67),

g) combining the DNA fragment of e) with DNA comprising sequences complementary to intergenic regions of genomic DNA of the cell under conditions in which hybridization between the DNA fragments and a sequence complementary to an intergenic region of the genomic DNA occurs (see figure 1),

h) identifying the one or more sequences complementary to the one or more intergenic regions of genomic DNA of f) to which the DNA fragment hybridizes whereby the region identified in g) is the region of the genome in the cell to which the protein of interest binds (see figure 1).

Mercola expressly states "For example, a region of a nucleic acid molecule that binds with a transcription factor can be within a gene, upstream of a gene or downstream of a gene (see column 14, lines 48-50)." The only reasonable interpretation of Mercola's teaching of regions "upstream" or "downstream" of a gene is regions that by definition are between genes and therefore "intergenic". Mercola therefore expressly teaches intergenic regions.

With regard to claims 1, Mercola teaches hybridization to cDNAs on a matrix (see figure 1), which is an express form of a microarray.

With regard to claims 15, 16, Mercola teaches the use of fluorescent labels such as Cy3 and Cy5 (see column 17, lines 60-65).

With regard to claims 2, Mercola teaches the use of cells which are eukaryotic (see column 11, line 23).

With regard to claims 3, Mercola teaches the use of DNA binding transcription factors (see column 11, line 6).

With regard to claims 4, Mercola teaches crosslinking with formaldehyde (see figure 1).

With regard to claims 5, Mercola teaches the use of antibodies to bind the protein of interest (see figure 1).

With regard to claims 6, 90 and 91, Mercola teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see figure 1).

With regard to claims 8, Mercola teaches the use of a control (see column 19, lines 23-25).

With regard to claims 17, Mercola teaches shearing the DNA to make fragments (see figure 1).

With regard to claims 87-89 and 92, Mercola expressly teaches the desirability of genomic DNA (see column 11, lines 5-10 and claim 3, which expressly recite genomic DNA).

Mercola expressly teaches the use of ordered microarrys (see column 18).

Mercola does not teach the use of two color fluorescence, with the use of a second label to control for hybridization of specific captured sequence and nonspecific captured sequence.

Hacia teaches the use of a two label system where one of the labels is Cy5-phycoerythrin (see page 3865, column 2).

Schena teaches the use of two colors of fluorescent labels to multiplex samples on microarrys (see page 301 to page 302).

With regard to claims 15 and 16, Schena expressly teaches fluorescent labeling, showing a Cy5 fluorescently labeled microarray in figure 3.

Schena teaches the use of microarrays to analyze genomic information (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent Cy5 dye of Hacia into the detection method of Mercola since Hacia notes "Two color analysis allows competitive hybridization between a reference standard and an unknown sample, improving the performance of the assay (see abstract)." So an ordinary practitioner, wishing to modify Mercola to obtain the benefits, known to the ordinary practitioner of a negative control sample (such as those taught by Mercola at column 19, lines 23-25) would have been motivated to use the two color system of Hacia since the two color system would improve signal specificity and accuracy as taught by Hacia (see page 3866, column 2). Further motivation is provided by Schena, who expressly indicates that fluorescent labeling is advantageous since "Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made

on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)." This same logic would apply to the method of Mercola, since an ordinary practitioner would recognize, from the motivation of Schena, that the use of two fluorescent labels would permit multiplexing the analysis under precisely the same conditions, eliminating many of the complicating factors in the analysis. Further motivation to use Cy5 is that minimal spectral overlap is imposed when this dye is used in combination with phycoerythrin as discussed by Hacia.

The ordinary practitioner is highly skilled in this art, at least a Ph.D. with years of experience as evidenced by the authors of the prior art. Dr. Schena is world renowned with a Ph.D. and 20 years of experience, Dr. Mercola is an MD and a Ph.D. who is a professor at the Stanley Kimmel Cancer Center and Dr. Hacia is a Ph.D with years of experience, who was an assistant professor at USC at the time of the invention. Given this high level of skill, the use of a two color control on a microarray would have been prima facie obvious to these ordinary practitioners at the time of the invention.

Response to Arguments

8. Applicant's arguments filed November 28, 2006 have been fully considered but they are not persuasive.

Applicant argues that Orlando does not teach a second labeled portion that is used as a control. This is simply incorrect as shown in the rejection above. Applicant

also argues that there is no teaching of intergenic regions. That is also incorrect as discussed in the rejection and claim interpretation above.

The arguments against the Mercola rejection are also not found persuasive for the same reasons, the teaching are present in the rejections.

Applicant is correct that cancellation of several claims renders certain rejections moot.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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Art Unit 1637
1/27/10